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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/015,822	BAKER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 28-35 and 38-40 are under consideration in the instant application.

Claim Rejections - 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 28-35 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 28-35 and 38-40 at pages 2-32 of the previous Office Action of 25 October 2006, pg 2-19 of the Office Action of 30 November 2005, at pg 3-12 of the Office Action of 25 April 2005, and at pg 3-8 of the Office Action of 04 November 2004.

Specifically, claims 28-35 and 38-40 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown of SEQ ID NO: 374, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 374, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited

under ATCC accession number 203465; wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

Applicant's arguments in the response submitted 27 January 2007, as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

To summarize, for utility of the claimed PRO1759 polypeptides, Applicant relies on the gene amplification data for the gene encoding the polypeptide. Applicant argues that Example 143 of the specification discloses that the PRO1759 gene is significantly overexpressed in colon and lung tumors as compared to normal control. Applicant asserts that the PRO1759 polypeptide is useful as a diagnostic marker and a therapeutic target for treatment for tumors. Briefly, it is the Examiner's position that the present specification fails to disclose the physiological significance of the PRO1759 polypeptide or what the correlation between PRO1759 DNA, PRO1759 mRNA and PRO1759 polypeptide expression is or the significance of any such correlation in colon and lung tumors. A specific benefit does not exist in currently available form because the skilled artisan would not know if the expression of the PRO1759 polypeptide would be upregulated, down-regulated, or unchanged in cancer. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO1795, the instant claimed invention is incomplete. Therefore, Applicant's assertion of the overexpression of the PRO1759 gene does not impute a specific and substantial utility to the PRO1759 polypeptide or antibodies.

Specific arguments are addressed below.

(i) At pg 2-3 of the Response, Applicant asserts that it was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Applicant states that Example 143 of the specification discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8. Applicant explains that a ΔCt value of at least 1.0 was observed for PRO1759 in at least three of the tumors listed in Table 8. Applicant argues that PRO1759 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or 2.16 fold or 2.85 fold amplification in lung tumors HF000842 and HF001296 and in colon tumor center HF000795. Applicant submits that the specification has not only disclosed that the DNA copy number for the gene encoding PRO1759 is increased in *three different lung tumors*, but has also quantified the degree of gene amplification observed in each of these lung tumors. Applicant cites the Declaration of Dr. Audrey Goddard and contends that absence any evidence to the contrary, the 2.16 to 2.85-fold amplification disclosed for the PRO1759 gene is significant. Applicant states that a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon). However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers. Further research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested

by the instant disclosure. It is not known whether PRO1759 is expressed in corresponding normal tissues, and what the relative levels of expression are. Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (see *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689)).

As discussed in the previous Office Action and reiterated herein, the declaration under 37 C.F.R. §1.132 by Dr. Goddard was fully considered in the Office Action of 25 April 2005. The Examiner maintains that the Goddard declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed polypeptides, which are encoded by the nucleic acid which is alleged to be significantly amplified in cancer. Applicant discusses the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number and that this increase is significant and useful. Applicant directs the Examiner to page 3 of the Dr. Goddard declaration that describes the gene amplification technique in the present application and references that attest to the use of this technique in diagnostic and prognostic fashion. This argument has been fully considered but is not deemed persuasive

because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1759 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in two types of cancer samples (lung, colon), to a minor degree (about 2.16 to 2.85 fold). No mutation or translocation of PRO1759 has been associated with any type of cancer versus normal tissue.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (cited in the Office Action of 25 April 2005) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Therefore, the Goddard declaration is not persuasive as it relates only to the issue of nucleic acid and not to the claimed subject matter, which is polypeptides, and further, *if* the claims were directed to nucleic acids, would still have not been persuasive.

(ii) At page 4 of the Response, Applicant asserts that the negative control taught in the specification was known in the art at the time of filing, and accepted as a true negative control as

demonstrated by use in peer reviewed publications, including Pennica et al. Applicant points out that Pennica explains the WISP copy number in each colon tumor DNA was compared with pooled normal DNA from 10 donors. Applicant contends that Pennica et al. use the same control for their gene amplification experiments as that described in the instant specification. Applicant submits that Pitti et al. (submitted with the Response of 02 February 2005) describe the analysis of DNA copy number in genomic DNA from primary tumors relative to pooled genomic DNA from peripheral blood leukocytes. Applicant argues that Bieche et al. (submitted with the Response of 02 February 2005) used normal leukocyte DNA derived from a small subset of breast cancer patients and note that the results of the study are consistent with those reported in the literature. Applicant concludes that the art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, although Pennica et al. and Pitti et al. compare gene amplification of specific genes in colon and lung tumors to pooled DNA from 10 healthy normal donors, Pennica et al. and Pitti et al. are not attempting to utilize the data generated from the experiments for diagnostic purposes (as is Example 143 of the instant application). Secondly, Bieche et al. is simply utilizing real-time PCR to validate an assay for the detection and determination of the copy numbers of the three most frequently amplified genes in breast tumors (*myc, ccnd1*, and *erbB2*). Bieche et al. compare the results for 108 breast tumors with previous Southern-blot data for the same samples (abstract; page 662, column 1). The genes studied by Bieche et al. were already well-known in the art to be amplified in breast cancer. Thus, it was not necessary to utilize matched normal tissue samples.

Regarding the instant application, the specification provides data purportedly showing a slight increase in DNA copy number in two different types of tumor tissue (lung and colon) of PRO1759. However, PRO1759 is novel and has not been characterized in the pre- or post-filing date art. It is not known whether PRO1759 is expressed in corresponding normal tissues, and what the relative levels of expression are. There is no structure/function analysis in the specification regarding the putative protein encoded by the PRO1759 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO1759 gene would confer any selective advantage on a cell expressing it. It has no known homology to any protein that would be expected to *confer a selective advantage* to a tumor cell. Additionally, gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments.

(iii) At page 5 of the Response, Applicant contends that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. Applicant states that amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Applicant's arguments have been fully considered but are not found to be persuasive. Aneuploidy is a feature of damaged tissue, and is commonly found in lung tissues, which are subject to constant environmental damage. It does not invariably or inevitably lead to cancer; rather, such damaged cells are generally removed by the body; the development of cancer is the

exception, as evidenced by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. The specification of the instant application asserts that since the nucleic acid encoding PRO1759 is slightly overexpressed in colon and lung tumor samples, the PRO1759 polypeptide may be used in the diagnostic determination of the presence of cancers. However, a positive result can also correlate with *damaged*, but not cancerous, lung and colon epithelium. Merely because aneuploidy may be an initial step in the *formation of cancer* does not equate with a substantial assertion of a diagnostic tool *for cancer* for the encoded PRO1759 protein.

(iv) At pages 6-7 and 13 of the 25 January 2007 Response, Applicant asserts that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Applicant argues that the references cited by the Examiner (Pennica et al, Chen et al., Haynes et al., Hu et al., Madoz-Gurpide et al., Celis et al., Steiner et al., and Feroze-Merzoug et al.) do not suffice to make a *prima facie* case that more likely than not generalized correlation does not exist between increased mRNA expression and increased polypeptide levels. Applicant states that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard.

Applicant's argument has been fully considered but is not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. In the previous Office Actions of 25 October 2006, 30 November 2005, 25 April 2005, and 04 November 2004, the Examiner made a *prima*

facie showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (Pennica et al., Sen et al., Chen et al., Haynes et al., Hu et al., Madoz-Gurpide et al., Celis et al., Steiner et al., and Feroze-Merzoug et al.). These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptides are not useful as cancer diagnostic agents. Essentially, Applicant has not provided evidence to demonstrate that gene amplification correlates with polypeptide over-expression or that PRO1759 polypeptide of the instant application is supported by a specific and asserted utility or a well established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response (see points (i)-(iii) and (v)-(xvi)). It is noted to Applicant that MPEP § 2107.02 (part VI) also states that "only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

(v) At the bottom of page 6 through page 7 of the Response, Applicant reiterates that teachings of Pennica are specific to *WISP* genes and say nothing about the correlation of gene amplification and protein expression in general. Applicant adds that Sen focuses on aneuploidy and changes in gene copy numbers in cancer, but says nothing about the correlation of gene amplification with protein expression.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons already made of record at pages 6-7 in the previous Office Action of 25 October 2006. It is noted that Applicant has not established a nexus between the DNA of instant invention and the PRO1759 protein. The skilled artisan would not reasonably assume that PRO1759 gene

amplification correlates with polypeptide overexpression in certain colon or lung tumors based on the disclosure regarding gene amplification without actually testing for PRO1759 polypeptide overexpression or that the PRO1759 polypeptide can be used as a cancer diagnostic. Applicant has not provided any testing of the role, activity, or expression of the PRO1759 polypeptide in cancer. The art as a whole teaches toward a *lack of expectation* of a correlation for a gene that is amplified consistent with the data proffered for PRO1759.

(vi) At page 8 of the Response, Applicant argues that Gygi et al. indicate a general trend of increased protein levels results from increased mRNA levels. Applicant asserts that while Gygi et al. may teach that protein levels cannot be accurately predicted from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels, a showing that MRNA levels can be used to "accurately predict" the precise levels of proteins expression is not required.

Applicant's arguments have been fully considered but are not found to be persuasive. While Gygi et al. does not address whether changes in mRNA levels will be reflected as observable changes in protein levels, the reference nonetheless demonstrates that observed mRNA levels do not necessarily correspond to observed protein levels. Gygi et al. state "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA

transcript analysis is insufficient" (abstract; pg 1727, top of col 2; pg 1730, concluding sentence). The Examiner is unable to locate where the Gygi et al. reference discusses "accurately predicting" the precise levels of protein expression. Applicant has not specifically pointed out this teaching in the reference.

(vii) At the bottom of page 8, Applicant contends that Futcher et al. note that Gygi et al. used an inappropriate correlation coefficient in the analysis of their data. Applicant also points out that Futcher et al. note that the two studies used different methods of measuring protein abundance. Applicant submits that the Gygi data shows a strong correlation for the most abundant proteins but a poor correlation for the least abundant proteins in their data set.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Futcher et al. conclude that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (pg 7368, col 1). Futcher et al. clearly emphasize that mRNA abundance might be utilized as a predictor of protein abundance only for abundant proteins. However, regarding the instant specification, one skilled in the art cannot determine if the polypeptide of PRO1759 is overexpressed simply based upon the gene amplification data in Example 143. There is no guidance in the specification as to how high the levels of overexpression are. If a clinician took a colon tissue sample from a patient with suspected colon cancer, what is the likelihood that when compared with normal tissue, the level of PRO1759 from the patient would be higher? How many samples would be needed? What sensitivity would be needed?

Furthermore, in the previous Office Action, the Examiner pointed out that Futcher et al. cites Gygi et al. who performed a similar study and generated similar data, but reaches a different

conclusion (mRNA abundance is a poor predictor of protein abundance). These two studies were only published a few months apart and clearly provide evidence as to the unpredictability in the art of predicting protein levels from mRNA levels.

(viii) Applicant indicates at page 9 of the Response that Feroze-Merzoug et al. looked at androgen regulated genes, which were not necessarily associated with cancer. Applicant indicates that even if the teaching of Feroze-Merzoug et al. accurately reflects the correlation between mRNA and protein, it does not apply to the lung and colon cancer diagnostic assays of the present application.

Applicant's arguments have been fully considered but are not found to be persuasive. Feroze-Merzoug et al. reviews recent mRNA and protein expression profiling studies performed in prostate cancer. The reference discloses that "downstream genes in the androgen pathway play a critical role in the development of hormone-refractory prostate cancer" (pg 166, col 1, 1st paragraph). Thus, even though Feroze-Merzoug et al. do not examine the expression of PRO1759 of the instant application, the teachings of Feroze-Merzoug et al. clearly indicate that mRNA levels do not predict protein levels. For example, Feroze-Merzoug et al. disclose that "there is evidence highlighting the disparity between mRNA transcript and protein expression levels" and that "it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1, 1st full paragraph).

Additionally, the instant specification does not establish a nexus between the DNA of instant invention and the PRO1759 protein or that PRO1759 mRNA levels are expressed at significantly higher levels compared with normal, matched tissue samples. Therefore, the skilled artisan would not reasonably assume that PRO1759 gene amplification correlates with

polypeptide overexpression in certain colon or lung tumors based on the disclosure regarding gene amplification without actually testing for PRO4329 polypeptide overexpression or that PRO1759 protein and PRO1759 antibodies can be used as a cancer diagnostic.

(viii) At the bottom of page 9 through the top of page 10 of the Response, Applicant indicates that Chen et al. has been previously addressed. Applicant reiterates that a review of the correlation coefficient data presented in the Chen et al. paper indicates that it is more likely than not increased mRNA expression correlates with increased protein expression.

Applicant's arguments have been fully considered but are not found to be persuasive. Chen et al. compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1759 mRNA or polypeptide is overexpressed in colon and lung tumors, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed PRO1759 polypeptides is not in currently available form, the asserted utility is not substantial.

(ix) At page 10 through page 11 of the Response, Applicant fails to see why the present specification must disclose the same amount and same type of information as in Beer et al. Applicant states that Beer et al. was submitted to show the reliability of microarray assay and the

existence of the mRNA/protein correlation. Applicant asserts that the Office personnel must treat as true a statement as fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such as statement. Applicant submits that one of ordinary skill in the art would not have a legitimate basis to doubt the credibility of the results of the present microarray assay because the Beer reference has established the reliability in general. Applicant states that Beer never suggests that microarray data must be confirmed by the protein expression.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Beer et al. (cited by Applicant in the Response of 01 June 2006) indicate that their results demonstrate that a gene-expression risk profile based on the genes most associated with patient survival-can distinguish stage I adenoscarcinomas and differentiate prognoses (abstract; pg 822, col 2, 3rd full paragraph). As discussed in the previous Office Action, Beer et al. used hierarchical clustering to examine similarities among lung adenocarcinomas in their patterns of gene expression and even identify "three clusters that showed significant differences with respect to tumor stage and tumor differentiation" (pg 822, 1st full paragraph). However, the Examiner could not locate a conclusion in Beer et al. that microarrays are a reliable measure of the expression levels of a gene. Secondly, Example 143 of the instant specification utilizes the 5' nuclease assay (TaqMan) to determine gene amplification, and not a microarray to determine mRNA expression (as in Beer). The instant specification does not disclose any special feature, stage, or prognosis, of colon and lung tumors that amplify or overexpress the PRO1795 gene compared to colon and lung tumors that do not amplify the PRO1759 gene. It is left to the

skilled artisan to determine the significance (if any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention. Additionally, although proteomics is a complementary technology to DNA microarrays, it is quite clear that the state of the art is such that gene amplification does not reliably correlate with polypeptide over-expression (see for example, Pennica et al., Hu et al., Haynes et al., Chen et al., and Godbout et al.) and polypeptide levels cannot be accurately predicted from mRNA levels (see for example, Madoz-Gurpide et al., Celis et al., and Feroze-Merzoug et al.). Beer et al. even complemented their DNA microarray expression studies with northern blot hybridization and immunohistochemistry experiments for three arbitrarily selected genes with high expression. However, the specification of the instant application does not complement the PRO1759 expression data with any protein studies. The skilled artisan would not reasonably assume that PRO1759 polypeptide is overexpressed in colon and lung tumors based on the disclosure regarding gene overexpression without actually testing for PRO1759 polypeptide overexpression.

(x) At page 11 of the Response, Applicant argues that Madoz-Gurpide et al., Celis et al., and Steiner et al. make clear that proteomic techniques are useful to obtain information beyond expression levels. Applicant states on page 12 of the Response that while this additional information may be useful in elucidating the detailed biological function of a protein, it is not required to establish utility of a protein as a marker for cancer because the claimed PRO1759 polypeptides can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the polypeptides. At page 12 of the Response, Applicant adds that significant

correlations between gene and protein expression are most likely to be observed for genes associated with cancer.

Applicant's argument has been fully considered but is not found to be persuasive. Additionally, although proteomics is a complementary technology to the determination of DNA expression levels, it is quite clear that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Celis et al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). Madoz-Gurpide state that "numerous alterations may occur in proteins that are not reflected in changes at the RNA level" (pg 53, 2nd full paragraph). Celis et al. also state that proteomics addresses problems that cannot be approached by DNA analysis, including relative abundance of the protein product (pg 6, top of col 2). Celis et al. cite two different groups, namely Anderson et al. and Orntoft et al., and indicate that each group had different results when comparing mRNA and protein levels. Celis et al. point out that Anderson et al. showed there is not a good correlation between mRNA and protein levels in human liver (pg 13, col 1, 2nd full paragraph) while Orntoft et al. found a good correlation between transcript and protein levels for highly abundant polypeptides (pg 13, col 1, 3rd full paragraph). Thus given the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels.

Additionally, although Applicant reiterates that the claimed PRO1759 polypeptides can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the polypeptides, the instant specification does not establish a nexus between the DNA of instant invention and the PRO1759 protein or that PRO1759 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, the skilled artisan would not reasonably assume that PRO1759 gene amplification correlates with polypeptide overexpression in certain colon or lung tumors based on the disclosure regarding gene amplification without actually testing for PRO4329 polypeptide overexpression or that PRO1759 protein and PRO1759 antibodies can be used as a cancer diagnostic.

(xi) At the bottom of page 11 of the Response, Applicant contends that Hu et al. did not look for a correlation between changes in mRNA and changes in protein levels, and therefore, their results are not contrary to Applicant's assertion that there is a correlation between the two. At page 12, Applicant argues that Hu et al. does not demonstrate the conclusion the PTO attempts to reach concerning a general lack of correlation between microarray data and biological significance. Applicant emphasizes that Applicant is not relying on any "biological role" that the PRO1759 polypeptide has in cancer for its asserted utility. Instead, Applicant is relying on the overexpression of PRO1759 in certain tumors as compared to their normal tissue counterparts.

Applicant's arguments have been fully considered but are not found to be persuasive. The asserted utility for the claimed PRO1759 polypeptides is based on Applicant's assertion that increased mRNA production leads to increased protein production. Although Hu et al. did not look at correlations between mRNA and protein, Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and

normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not establish a nexus between the DNA of instant invention and the PRO1759 protein or that PRO1759 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, the skilled artisan would not reasonably assume that PRO1759 gene amplification correlates with polypeptide overexpression in certain colon or lung tumors based on the disclosure regarding gene amplification without actually testing for PRO4329 polypeptide overexpression or that PRO1759 protein and PRO1759 antibodies can be used as a cancer diagnostic. Also, Hu et al. provides conclusions based on many research efforts. If anything, their conclusions are even more probative than the conclusions based on a smaller scale study.

(xii) At the bottom of page 13 of the Response of 25 January 2007, Applicant asserts that the Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. Applicant contends that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. Applicant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), Haynes et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al., and Celis et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptide is not useful as a cancer diagnostic agent.

(xiii) Applicant submits at page 14 of the Response that Orntoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification correlates with increased mRNA expression. At pages 14 and 17-18 of the Response, Applicant points to the Polakis declarations (submitted under 37 C.F.R. § 1.132 on 02 February 2005 and 07 August 2006) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Finally, Applicant concludes that, while there may be exceptions, there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the issue in the instant application is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. There is no demonstration of *any* mRNA level for PRO1759, either in the specification or in *any* of the numerous declarations that have been submitted, hence the theoretical correlation of mRNA with protein is not

probative. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Hu et al., Haynes et al., Chen et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al, Celis et al.

Applicant's arguments of the Orntoft reference were fully answered at page 20 of the previous Office Action and at pages 10-11 of the Office Action of 25 April 2005. Applicant again asserts that the amplification levels for PRO1759, which are now alleged to be between 2.16 and 2.85 fold, are significantly higher than those of Orntoft. This argument has been fully considered but is not deemed persuasive because as previously stated, the methodology used by Orntoft is different from that of Applicant. What is significant remains that the levels of amplification observed by Applicant are consistent with aneuploidy, which is a known feature of cancerous cells, and that such amplification is not accepted in the art as being predictive of increased protein expression, which increased expression would be essential for the claimed polypeptides to have the asserted utility. Additionally, the Examiner was unable to locate a conclusion in Orntoft et al. that they found markers associated with cancer malignancy (as asserted by Applicant at the top of page of the Response of 25 January 2007). It must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). Orntoft et al. only compared genes

from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue.

(xiv) At the bottom of page 16 of the Response, Applicant argues that the Examiner's position is inconsistent with the Hyman reference. Applicant's arguments have been fully considered but are not found to be persuasive for reasons already made of record at pages 20-24 of previous Office Action. Although Hyman was comparing genomic amplification to mRNA levels, those genes were *highly amplified,* which PRO1759 is not. The Examiner maintains that the levels of amplification shown from PRO1759 were not of a high enough level to be predictive of protein increases, for reasons amply of record. The Examiner reiterates that at pages 517-519 of the specification, it is disclosed that nucleic acids encoding PRO1759 had a ΔCt value of at least 1.0 for one primary lung tumor (HF-000840), one primary colon tumor (HF-000795), and HF001296. It remains that Hyman teaches that 44% (fewer than half) of *highly amplified* genes were overexpressed, and only 10.5% of overexpressed genes were found to be highly amplified. Simply put, Hyman teaches that *if* the gene is highly amplified there is still a less than 50%, or 44% chance that the mRNA will be similarly amplified, and that if one approaches the problem from the other end, of the genes *known* to be overexpressed in breast cancer, only 10.5% of that overexpression can be attributed to gene amplification. Accordingly, it would seem more likely than not that the PRO1759 protein would *not* be overexpressed in cancer, based upon (a) the low levels of amplification in a minority of tumor cells tested, and (b) Hyman's teaching that even *if* there were high levels of amplification, it would still be more likely than not that expression would *not* correlate to amplification.

(xv) At page 17 of the Response, Applicant addresses the Pollack et al. reference and states that the art is consistent in finding that gene amplification levels of at least 2-fold, regardless of the measurement procedures, are reliably correlated with increased mRNA expression.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons already made of record at page 20-22 of the previous Office Action. Pollack et al., using CGH technology, concentrate on large chromosome regions showing high amplification (pg 12965). However, Pollack et al. did not investigate or show a relationship with gene amplification and polypeptide expression. In fact, the authors caution that elevated expression of an amplified gene cannot alone be considered strong independent evidence of candidate oncogene's role in tumorigenesis (pg 12968). It remains that for the PRO1759 gene, a 2.16 to 2.85 fold amplification of the genomic DNA has been shown for three tumors/tumor cell lines. There has been *no* demonstration of the existence of any mRNA nor the level thereof, nor any demonstration of any protein expression, in any cell or tissue, under any conditions. In view of the cited art, the Examiner maintains that the data in the specification would not be considered by one skilled in the art to be reasonably predictive that the claimed proteins have diagnostic or prognostic utility.

(xvi) At page 19 of the Response, Applicant argues that Meric summarizes the translation regulation of cancer cells. Applicant states that Meric never suggest that the translation of a cancer gene is suppressed in cancer in general, and therefore, an increased mRNA levels will not yield an increased protein levels. Applicant argues that Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to its normal counterpart.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, Meric et al. disclose that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teach that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). For example, Meric et al. indicate that variations in the mRNA sequence of the tumor suppressor, BRCA1, leads to a *decrease* in translation efficiency (pg 74, col 1). Meric et al. also point out that a mutation in cyclin-dependent kinase inhibitor 2A (also a tumor suppressor) gives rise to a novel AUG translation initiation codon, generating an upstream open reading frame that competes for scanning ribosomes and *decreases* the translation from the wild-type AUG (pg 74, col 1). Meric et al. also teaches that in patients with multiple myeloma, a C→T mutation in the c-myc IRES causes an *enhanced* initiation of translation (pg 74, col 1). Thus, Meric et al. teaches that the translation efficiency of individual mRNA molecules which play a role in cancer may be decreased or enhanced in cancer cells as compared to normal cells. Meric et al. clearly evidences that polypeptide levels cannot be accurately predicted from mRNA levels.

(xvii) Applicant contends at page 20 of the Response that the references submitted on 07 August 2006 demonstrate a trend of correlation found across proteins in general, and that this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues, under numerous biological conditions. Applicant also argues that those few references that actually looked at gene

amplification did find a correlation between gene amplification and increased mRNA and protein expression levels. At page 21 of the Response, Applicant submits that Bea et al. clearly supports Applicant's assertion that gene amplification is correlated with increased mRNA and protein expression. Applicant states that the passage cited by the Examiner from Godbout in the previous Office Action is based upon two references from 1987 and 1992. Applicant indicates that three more recent references were made of record (Ornoft et al., Hyman et al., Pollack et al.) which collectively teach in general, gene amplification increases mRNA expression. Applicant also states that as explained in the Supplemental Information accompanying the Li article (Exhibit A), genes were considered to be amplified if they had a copy number ratio of at least 1.40. Applicant contends that by using a substantially lower threshold for considering a gene to be amplified, Li et al. would have identified a number of genes that were not in fact significantly amplified.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant's arguments have been fully considered but are not found to be persuasive. The major issue in this rejection is the lack of correlation between PRO1759 DNA, PRO1759 mRNA and PRO1759 polypeptide expression and the significance of any such correlation in colon and lung tumors. A secondary issue, and the one that applicants are giving the vast majority of their attention, is the issue of whether or not elevated mRNA levels, *if they were observed,* would be predictive of elevated protein levels. In the response filed 07 August 2006, Applicant has cited no fewer than 149 newly submitted references in support of their position that mRNA levels are predictive of protein. However, Applicant is reminded that all of Applicant's newly cited

references (with the exception of Bea et al. and Godbout et al.) do not measure gene amplification, which is the assay utilized in Example 143 of the instant specification. Additionally, an in-depth evaluation and discussion of 149 references that are not directly drawn to either the issue of the correlation between gene amplification, mRNA, and protein expression or to PRO1759 in particular is beyond the USPTO's resources. The mere existence of 149 references that do not provide consistent teachings to support Applicant's case is evidence of the unpredictability in the art, the type of unpredictability that leads to the conclusion that the instant specification represents a mere invitation to experiment to determine a utility for the claimed PRO1759 polypeptide.

Reviewing Bea et al., Applicant argues that the issue is not how common gene amplification is, nor whether mRNA and protein overexpression is always or typically caused by gene amplification, but rather, whether gene amplification when present typically leads to mRNA and protein overexpression. It is noted that the study of Bea et al. is directed to one particular gene (BMI-I) and specific cancer types and does not accurately describe general trends. Bea et al. also performed Southern blots, RT-PCR, and Western blots to determine the relationship between gene amplification, mRNA expression, and protein expression, which is unlike Example 143 of the instant specification.

It is noted that Orntoft et al., Hyman et al., and Pollack et al. were published in 2002 (post-filing date publications) and utilize different methods from the instant specification and Godbout et al. The Examiner has discussed these references extensively in points (xiii)-(xv) above and at pages 20-22 of the previous Office Action of 25 October 2006 and at pages 14-18 of the Office Action of 06 October 2005. Although these references generally compare genomic

amplification to mRNA levels, those genes studied were *highly amplified,* which PRO1759 is not. The Examiner maintains that the levels of amplification shown for PRO1759 were not of a high enough level to be predictive of protein increases, for reasons amply of record. Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA and an associated rise in level of the encoded protein. Additionally, even Orntoft et al. noted that mRNA and protein levels did not always correspond. Based upon this disclosure, the skilled artisan would recognize the unpredictability in the art of predicting protein levels from mRNA and DNA.

As discussed in the previous Office Action, Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. clearly state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*"

In conclusion, in the instant case, the asserted utility that PRO1759 polypeptides are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO1759 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO1759 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels

(Pennica et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy tissue or cancerous tissue (see Haynes et al., Hu et al., Hanna et al., Chen et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al, Celis et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not the claimed PRO1759 polypeptides can be used as a cancer diagnostic agent.

35 U.S.C. § 112, first paragraph (Enablement)

2. Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pg 32 of the previous Office Action of 25 October 2006, at pg 19-20 of the s Office Action of 06 October 2005, pg 12-15 of the Office Action of 25 April 2005 and at pg 8-11 of the Office Action of 04 November 2004.

Applicant's arguments (25 January 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a credible, substantial, and asserted utility has been disclosed above for the polypeptide PRO1759. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1759 polypeptide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that

the instant specification is required to teach one skilled in the art how to make and use the PRO1759 polypeptide.

3. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-32 and 39-40 would remain rejected under 35 U.S.C. § 112, first paragraph. It is noted that specific issues of claims 28-32 and 39-40 (recitation of percent identity), were discussed under 35 U.S.C. § 112, first paragraph at pg 33-34 of the previous Office Action (25 October 2006), pg 20-22 of the previous Office Action (06 October 2005), at pg 13-15 of the Office Action of 25 April 2005, and at pg 9-11 of the Office Action of 04 November 2004.

Applicant maintains the position that claims 28-32 and 39-40 satisfy the enablement requirement for the reasons previously set forth in Applicant's responses. Applicant's arguments have been fully considered and the Examiner maintains the rejection for reasons already made of record.

Essentially, the specification does not teach any variant, fragment, or derivative of the PRO1759 polypeptide other than the full-length amino acid sequence of SEQ ID NO: 374. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives (including the extracellular domain) recited in the claims. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large

quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity.

Proper analysis of the Wands factors was provided in the previous Office Actions. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, first paragraph (written description)

4. Claims 28-32 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 34-35 of the previous Office Action (25 October 2006), at pg 22-25 of the Office Action of 06 October 2005, at pg 15 of the Office Action of 25 April 2005 and at pg 11-13 of the Office Action of 04 November 2004.

Applicant maintains the position that claims 28-32 and 39-40 satisfy the written description requirement for the reasons previously set forth in Applicant's responses. Applicant's arguments have been fully considered and the Examiner maintains the rejection for

reasons already made of record.

Essentially, Applicant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 374, that still retain the function of SEQ ID NO: 374. Nor has Applicant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 374, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 374. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO1759 polypeptides, and therefore, would not know how to make or use them. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity, a requirement that the sequence be native, and a requirement that the encoding nucleic acids are amplified in lung or colon tumors. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. Additionally, there is the issue of whether or not the single disclosed embodiment is actually amplified in lung or colon tumors (see rejection under 35 U.S.C. §§ 101 and 112, first paragraph, above). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

The rejections of claims 28-35 and 38-40 under 35 U.S.C. § 101 and § 112, first paragraph (utility, enablement) have been made and maintained in the previous four Office Actions. Essentially, Applicant asserts that the PRO1759 polypeptide is useful as a diagnostic marker for colon and lung tumors. It is the Examiner's position that the present specification fails to disclose the physiological significance of the PRO1759 polypeptide or what the

correlation between PRO1759 DNA, PRO1759 mRNA and PRO1759 polypeptide expression is or the significance of any such correlation in colon and lung tumors. The state of the art has been cited and found to support both positions. It is the examiners opinion that the issue has been fully developed and, given the mixed teachings of the art, the examiner maintains that gene amplification of PRO1759 is not predictive of any correlation between the polypeptide and colon and lung tumors.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
03 April 2007

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER